

OPTOMETRY

Resistance to ocular antibiotics: an overview

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The introduction of new antibiotic compounds into therapy initiates the development of resistance by the target bacteria. Resistance increases the risk of treatment failure with potentially serious consequences. Local application of antibacterial compounds to the eyes may lead to bacterial resistance in bacterial isolates from the eyes. The incidence of resistant strains of common pathogens is probably increasing. As compounds can be absorbed into the systemic circulation following ocular administration, the subsequent low concentrations in the blood could provide the selective pressure for the survival of resistant bacteria in the body. Despite this possibility, there are no reports of systemic resistance in bacteria following ocular administration of antibacterial compounds. All health-care professionals should be concerned about this possibility and continue to use these important compounds with respect.

Key words: aminoglycosides, antibiotics, bacterial resistance, chloramphenicol, fluoroquinolones

Infectious diseases have been a major cause of death throughout history. The changing causes of mortality in Australia over the past century have been documented in a recent report from the Australian Institute of Health and Welfare.¹ In Australia, the death rate in males from infectious diseases fell from 283 deaths per 100,000 population in 1907 to about six in 1980, after which it almost doubled to 11 in 2000. In contrast, the death rate for circulatory diseases increased from 437 per 100,000 of population in 1907 to 1,020 in 1968 before falling to 319 in 2000. For females, the death rate from infectious diseases fell from 230 in 1907 to four per 100,000 population in 1980, before increasing to seven in 2000. In the same period, the average life expectancy at birth increased by 23.6 years for males, from

53.8 years in 1900 to 77.4 in 2000 and by 25.1 years for females, from 57.5 to 82.6.

Classical medical teaching by Hippocrates and later Galen supported the concept that infections were caused by chemical miasmata (unhealthy emanations) arising from swamps and unburied corpses. Treatment was by removal of the miasmata by ringing bells in the open and letting birds fly around inside rooms. An early example of a more rational approach was the decision in 1647 by the town councillors of Aberdeen in Scotland to command the poisoning of rats and mice to reduce the spread of plague; the last case of bubonic plague in Scotland was in 1648. The discovery of bacteria as the causative agents of infection took several centuries. In 1683, Anton van Leeuwenhoek of Delft wrote to the Royal Society describing the

appearance of minute ‘animalcules’ under the microscope he had invented. Louis Pasteur in 1861 demonstrated that fermentation failed to take place when organisms from the air were excluded from heat-sterilised liquids. Robert Koch received the Nobel Prize in 1905 following his discoveries of the causative organisms for anthrax (1876), tuberculosis (1882) and cholera (1883). Koch is one of many outstanding scientists who have been awarded the Nobel Prize for their outstanding contributions to understanding pathogens.²

DEVELOPMENT OF ANTIBACTERIAL COMPOUNDS

The use of chemicals to selectively control infections is a relatively recent advance in

medicine. Early attempts to produce drugs with selective toxicity were unsuccessful. At the start of the 20th Century, Paul Ehrlich (Nobel Prize 1908) searched for compounds to treat trypanosomiasis (sleeping sickness in man), a protozoal infection; the most effective compound was an organic arsenical, salvarsan. In 1910, salvarsan was shown to cure syphilis in man and this drug was the drug of choice until 1945 when it was completely replaced by the less toxic and more potent penicillins. The first edition of Goodman and Gilman's textbook on *The pharmacological basis of therapeutics* in 1941 devotes more than 30 pages to the 'important and indispensable' organic arsenicals, which penicillins made redundant within a decade. The first successful synthetic drug against bacteria was the dye prontosil, developed in 1933 by Gerhard Domagk (Nobel Prize, 1939) as an effective treatment against streptococcal infections in mice and later in humans (including his daughter as one of the first patients). Prontosil was a pro-drug, metabolised to the sulphonamide, sulphanilamide. The development of the penicillins from Alexander Fleming in 1928 to Howard Florey and Ernst Chain at Oxford in the 1940s is widely known.³ The development of the antibiotics has been the subject of many books, including analysis of the impact of bacterial resistance.⁴

The key prerequisite for a chemical compound to inhibit or kill parasites is selectivity. Such selective toxicity depends on the discovery of biochemical differences between the host and the pathogen that can be exploited, so that the drug is toxic to the pathogen but innocuous to the host.⁵ There are three general classes of biochemical reactions that are potential targets: class I reactions that utilise glucose to produce ATP and simple carbon compounds, class II reactions utilising energy and class I compounds to make small molecules such as amino acids and lastly, class III reactions that convert small molecules into macromolecules such as proteins, nucleic acids and peptidoglycans.⁵ Class I reactions are not promising targets, as they are similar in humans and pathogens and show redundancy; class II and III

reactions are targets for all commonly used antibacterial drugs.⁵

There are four mechanisms of action on class II and III reactions that have been exploited to provide selective toxicity for pathogens. These mechanisms with drug examples are:

1. interference with cell wall synthesis (penicillins and cephalosporins)
2. inhibition of protein synthesis (chloramphenicol, tetracyclines, macrolides such as erythromycin, aminoglycosides such as gentamicin)
3. inhibition of key metabolic pathways (sulphonamides, trimethoprim)
4. interference with nucleic acids (fluoroquinolones such as ciprofloxacin and ofloxacin, antiviral compounds such as vidarabine and acyclovir).⁵

The most widely used ocular antibiotics are the fluoroquinolones, chloramphenicol and the aminoglycosides, such as gentamicin. The fluoroquinolones inhibit topoisomerase II, the enzyme that permits replication by producing a negative supercoil in DNA; chloramphenicol inhibits transpeptidation during growth of the peptide chain, while the aminoglycosides block protein synthesis following misreading of the RNA in the ribosome.⁵

DEVELOPMENT OF BACTERIAL RESISTANCE

The paradox of anti-infective treatment is that the introduction of newer, effective antibiotics into clinical medicine initiates the development of resistance, leading to a loss of effectiveness of the new drug. Resistance is defined as a significant increase in the drug concentrations in the blood needed to inhibit bacterial growth or cause bacterial death. The development of resistance should be expected from the evolutionary principle that organisms adapt genetically to changes in their environment. The short generation time and the presence of large numbers of bacteria allow rapid adaptation. Almost all *Staphylococcus* strains were susceptible to the penicillins, when they were introduced in the early 1940s. Resistance was first reported in 1944 and now virtually all strains are

resistant to the natural penicillins, aminopenicillins and antipseudomonal penicillins.³ Further developments have been the emergence of methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococci (VRE) and fully vancomycin-resistant strains (VRSA) with their associated health risks.⁶ Bacterial resistance may result in treatment failure, possibly increasing mortality rates and placing an increased burden on health-care facilities. The potential costs of health-care-acquired infections are enormous, with suggestions that MRSA alone increases hospital costs annually by between US\$1.5 and US\$4.2 billion in the USA and £3 billion in the UK.⁷ Despite these costs, the evidence suggests that control is highly cost-effective.⁷

Bacteria have developed complex biochemical mechanisms leading to resistance.⁸⁻¹⁰ The four major biochemical mechanisms of antibiotic resistance are alteration of the target site, enzymatic inactivation or modification of the compound, decreased uptake or increased efflux of the antibiotic compound and the development of bypass pathways.⁹ Some examples are alterations in the target protein for the aminoglycosides and macrolides, upregulation of the enzymes that inactivate the penicillins, the β -lactamases, downregulation of membrane proteins that the antibiotic compound requires for cell entry, such as OmpF in *E. coli* for entry of chloramphenicol, tetracyclines and quinolones, or upregulation of pumps that expel the antibiotic drug, such as the fluoroquinolones, from the cell, and the development of bypass pathways such as expression of the alternative penicillin binding protein (PBP2a) by MRSA.^{8,9} Bacteria may also develop resistance through acquisition of genetic material from other resistant organisms, usually by conjugation or transformation. Three case studies of the emergence of drug resistance, often to several different compounds at the same time, illustrate the different mechanisms by which resistant bacteria develop.⁸

Bacterial resistance develops to the commonly used ocular antibiotics, the fluoroquinolones, the aminoglycosides and

chloramphenicol, when used for systemic infections but the mechanisms are very different. Recent studies have shown increasing resistance to systemic use of nalidixic acid, a quinolone, in *Salmonella enterica* isolates in Korea¹¹ and the isolation of strains of *Vibrio fluvalis* resistant to nalidixic acid and ciprofloxacin in India.¹² Two mechanisms contribute to the development of resistance to fluoroquinolones: amino acid mutations in DNA gyrase and topoisomerase IV and over-production of the AcrAB efflux pump encoded by CmeABC.^{13,14} Bacteria with the amino acid mutations do not have the binding site for the fluoroquinolones; for example, a single point mutation (change of threonine to isoleucine at codon 86) caused a 128-fold increase in the minimal inhibitory concentration for ciprofloxacin.¹⁴ Over-expression of the efflux pump allows the bacteria to remove the antibacterial compound, resulting in bacterial survival. Current studies on the mechanisms of resistance may allow the development of chemicals to prevent resistance. An example is the role of the repressor protein LexA and the associated derepression of three specialised DNA polymerases in the evolution of resistance to ciprofloxacin, demonstrating that LexA cleavage and polymerase derepression are required for the evolution of resistance.¹⁵ Thus, compounds that inhibit LexA and the DNA polymerases should efficiently prevent the development of fluoroquinolone resistance.

In bacteria, especially Gram-negative bacteria, chloramphenicol is inactivated by the enzyme, chloramphenicol acetyltransferase. This resistance is borne by plasmids, defined as closed loops of DNA free in the bacterial cytoplasm that can replicate on their own. These plasmids often confer multi-drug resistance to the bacteria, for example the resistance of *Salmonella enterica* to ampicillin, streptomycin, sulphonamides and tetracyclines as well as chloramphenicol.¹⁶ Plasmids may also be involved in inactivation of aminoglycosides, which usually occurs by phosphorylation with kinases, adenylation with O-adenyltransferases or acetylation with N-acetyltransferases.¹⁶

BACTERIAL RESISTANCE IN OCULAR ISOLATES

Fluoroquinolones have been in widespread use as topical treatment for ocular infections since about 1990. Resistance to ciprofloxacin in ocular isolates of *Staphylococcus aureus* from patients with bacterial keratitis in Pittsburgh showed an increase from 5.8 per cent in 1993 to 35.0 per cent in 1997.¹⁷ In contrast, a retrospective review of 1,312 bacterial isolates from patients with keratitis in London between 1984 and 1999, including 33.4 per cent with *S. aureus*, did not show an increased proportion of isolates resistant to ofloxacin, but rather a significant increase in chloramphenicol resistance in Gram-negative bacteria.¹⁸ High susceptibility to the fluoroquinolones (90 to 95 per cent) has been reported in ocular bacterial isolates from 1985 to 2000 in São Paulo, Brazil.¹⁹ Of 532 isolates from European centres during 2001 and 2002, 5.5 per cent were resistant to the new fluoroquinolone, gatifloxacin, 11.7 per cent were resistant to ofloxacin and 12.4 per cent were resistant to ciprofloxacin.²⁰ The introduction of new fluoroquinolones, such as gatifloxacin appears to delay but not to prevent the development of resistance. The incidence of resistance to ciprofloxacin in methicillin-sensitive *S. aureus* isolates from ocular infections was eight per cent in 1990 to 1995 but increased to 20.7 per cent in isolates from 1996 to 2001.²¹ Further, the resistance to ciprofloxacin in methicillin-resistant *S. aureus* was 55.8 per cent in 1990 to 1995 and 83.7 per cent in 1996 to 2001. In these isolates, gentamicin susceptibility remained high at 99 per cent for methicillin-sensitive isolates and 86 per cent for methicillin-resistant isolates.²¹ High rates of resistance of methicillin-resistant *S. aureus* in ocular isolates to gatifloxacin (71 per cent), moxifloxacin (68 per cent), ciprofloxacin and ofloxacin (both 94 per cent) contrasted with complete sensitivity of these isolates to vancomycin and the low incidence of resistance (three per cent) to gentamicin.²² Methicillin-resistant *S. aureus* ocular infections are still an infrequent cause of eye infections overall, accounting for three per cent of

S. aureus infections in a major UK ophthalmic hospital,²³ although methicillin-resistant *S. aureus* were present in 57 per cent of conjunctival bacterial isolates from elderly patients in Japan.²⁴ In the UK study, all methicillin-resistant isolates were sensitive to chloramphenicol, while 81 per cent of isolates in the Japanese study were sensitive to chloramphenicol. A recent case study reported community-acquired methicillin-resistant *S. aureus* in chronic dacryocystitis in an 8.5-month-old boy.²⁵ Bacterial cultures showed sensitivity to gentamicin and vancomycin and resistance to amoxicillin and erythromycin.²⁵

Resistance to chloramphenicol has been reported in these studies. The sensitivity of *S. aureus* isolates was 85 per cent in corneal samples and 92 per cent in conjunctival samples in Brazil,¹⁹ while 14.1 per cent of ocular samples were resistant to chloramphenicol in Europe.²⁰ Both studies tested the sensitivity to gentamicin showing 72 per cent of *S. aureus* isolates from the cornea and 79 per cent from conjunctival isolates were sensitive in 1997 to 2000²⁴ and that 24.3 per cent of isolates were resistant.²⁰

It is worth noting that these definitions of resistance are based on results from standard routine tests from clinical microbiology laboratories and interpreted using achievable blood concentrations of the particular antibiotic. Direct application of topical antibacterial agents to the eye should result in initial high concentrations, much greater than those achieved in the blood and much higher than minimal inhibitory concentrations for most bacteria.²⁶ However, these high concentrations will dissipate much more rapidly than in the blood.²⁶ The pharmacokinetics of antibacterial compounds at the ocular surface remains under-researched.

POTENTIAL FOR SYSTEMIC RESISTANCE AFTER OCULAR ADMINISTRATION

Thus, resistance has been reported widely with use of the fluoroquinolones, the aminoglycosides and chloramphenicol, both for systemic and ocular treatment. The key question becomes whether drug use in the

eyes can produce systemic resistance and potentially failure of systemic antibacterial therapy. In addition to the development of resistance by bacteria, the prerequisite for this to occur is the absorption of drugs into the body after ocular administration.

After oral administration (for example, swallowing a tablet), the most popular route of drug administration, drugs pass from the stomach and intestine across the stomach or intestinal wall to the blood vessels before distribution to the rest of the body. To be absorbed, drugs need both water and lipid solubility; water solubility in the gastrointestinal contents and blood and lipid solubility to pass across the lipid layer of the cells that form the wall of the gastrointestinal tract. Many drugs such as aspirin and codeine are partly ionised depending on the pH of the solution that the drug is in, for example, aspirin is much more ionised in the acidic environment of the stomach than in the relatively neutral pH of the blood. Gentamicin demonstrates the necessity for both lipid and water solubility for oral absorption. This compound is extremely water-soluble with effectively no solubility in the lipid layers. As such, it is orally inactive and must be given by intravenous injection to achieve antibacterial concentrations in the blood.

Passage of drugs into the bloodstream following topical application to the eyes will also follow the same principles. There is nothing unique about drug transport across the eyes. When given topically to the eyes, an extremely water soluble compound, such as gentamicin, will produce localised effects on the surface of the eye but very little to no systemic absorption and thus no propensity to produce unwanted systemic effects, including the development of resistance. On the other hand, lipid-soluble compounds should be expected to enter the systemic circulation following topical administration to the eyes. A therapeutic or toxic systemic response will occur only if sufficient drug has been absorbed. Thus, the dose given will also play a major role in the determination of adverse effects.

These concepts can be demonstrated by the β -adrenoceptor antagonist, timolol, used as eye-drops for the treatment of

glaucoma. Adverse systemic effects from timolol eye drops have been reported, especially in the elderly, and include congestive heart failure, arrhythmias, sinus arrest, bronchospasm, central nervous system effects such as dizziness, depression, nightmares, headache, somnolence, insomnia, tinnitus, bizarre dreams and dyslipidaemia.²⁷ The *Australian Medicines Handbook* (2003) includes bradycardia as common (one to 10 per cent incidence) following the use of timolol eye drops with the following adverse effects as infrequent (less than one per cent incidence): hypotension, syncope, impotence, decreased libido, fatigue, confusion, hallucinations, bronchospasm. It is relevant to note here that glaucoma is much more prevalent in the older population; other concurrent disease states associated with the ageing population may also cause these responses. It is not possible to compare the doses used for ocular and oral therapy as timolol is available only for ocular use. One drop of timolol 0.5 per cent twice daily is a daily dose of about 0.5 mg; in contrast, the recommended oral dose for metoprolol in the treatment of hypertension is 50 to 100 mg daily.

Chloramphenicol is orally active and so can pass across lipid membranes. The manufacturer of chloramphenicol, Pfizer Pty Ltd, has supplied the following comment for inclusion in the Australian Prescription Products Guide: that 'Bone marrow hypoplasia, including aplastic anaemia and death, has been reported following local application of chloramphenicol'. Again, the different concentrations need to be considered: chloramphenicol eye-drops given as two drops two- to six-hourly will produce a daily dose of two to 10 mg, while the recommended oral dose of chloramphenicol for typhoid fever is one gram six-hourly or four grams each day. A similar difference in dosage applies for ciprofloxacin: 0.3 per cent eye-drops given as two drops four-hourly produces a daily dose of about two milligrams, while the recommended treatment for bronchial infections is 500 mg every 12 hours (one gram per day).

Thus, antibacterial compounds with some lipid solubility, such as the fluoroqui-

nolones and chloramphenicol should be expected to pass into the systemic circulation after ocular administration, to give low concentrations in the circulation. Such low antibiotic concentrations following ocular administration could provide the selective pressure for resistant bacteria to survive. A thorough search of the PubMed database did not produce any reports of systemic resistance produced by ocular application of antibacterial compounds such as gentamicin, tobramycin, chloramphenicol, ciprofloxacin or ofloxacin. In principle, short-term treatment, suggested to be the norm by optometrists, should produce less resistance than long-term treatment with antibacterial eye-drops.

STRATEGIES TO DEAL WITH BACTERIAL RESISTANCE

Antibiotic treatment and the development of bacterial resistance are not confined to ocular infections and so concepts developed for systemic infections may be useful for the control of ocular infections. The *Therapeutic Guidelines* series provides an independent consensus and interpretation of clinical evidence by an expert Australian group of experienced clinicians and pharmacists. One of these volumes, the *Antibiotic Guidelines*,²⁸ provides useful suggestions for treatment of pathogens. The evaluation of an inadequate response to antibiotic treatment is complex; an algorithm has recently been provided as an approach to apparent antibiotic failure.²⁹

The discovery of effective and safe antibiotics over the past 50 to 70 years may lead to the complacent view that new antibiotics will always be available to combat new infectious diseases. This may be possible if exciting new technologies, including genomics and structural biology, are used to extend the treatment options.³⁰ The problems of bacterial resistance are remarkably complex; a very interesting collection of viewpoints has just been published until the title 'Anti-infective research and development—problems, challenges, and solutions' in *Lancet Infectious Diseases*.³¹

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